Notice of Allowability	Application No.	Applicant(s)	
	09/869,595	SIPPEL ET AL.	
	Examiner	Art Unit	
	Daniel C. Gamett, PhD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *07/10/2007*.

2. ☒ The allowed claim(s) is/are *1,2,10,15-19,22,23,25-28,30-37,40-43,61-63,67-70,79,80 and 83-85*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☒ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *10/12/07* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Dr. Sagun KC on 10/12/07.

In the claims—

Claim 1. A fusion protein comprising at least three domains, wherein
a first domain mediates a membrane localization of the fusion protein in a cellular context, wherein the signal of said membrane localization comprises an amino acid sequence which comprises a farnesylation signal or prenylation signal,
- a second domain has a ligand-binding function and comprises an amino acid sequence
which comprises the receptor portion of a steroid receptor, and
- a third domain which comprises an amino sequence which comprises a Ras protein that is able to activate a signal pathway connected to a ~~Rasprotein~~ Ras protein in a cell, wherein when there is a lack of binding to the second domain of said fusion protein, the third domain cannot exert its activity to activate a signal pathway connected to a Ras protein in a cell, despite membrane localization, but when there is binding of ligand to the second domain of said fusion protein, said signalling pathway is activated.

Claims 11-13. cancelled

Claim 29. cancelled

Claim 35. A eukaryotic cell as claimed in claim 34, which is immobilized on ~~biochips~~ a biochip.

Claim 36. An *in vivo* assay for determining the suitability of a test substance as ligand for a receptor section of a steroid receptor, comprising:

(a) contacting the test substance with cells as claimed in claim 23 under conditions with which a signal pathway connected to a Ras protein cannot be activated in the cells in the absence of the fusion protein, where the fusion protein present in the cells contains a second domain comprising said receptor section, and a third domain which, when there is binding of ligand to the second domain, is able to activate the inactive signal pathway connected to a Ras protein,
(b) ~~investigating~~ determining whether activation of the signal pathway connected to a Ras protein has taken place, where detection of the activation of the signal pathway connected to a Ras protein indicates the ability of the test substance to bind to the second domain of the fusion protein and thus to the receptor section.

Claim 38. cancelled

Claim 40. An assay as claimed in claim 36, wherein the test substance is ~~a naturally occurring substance which is~~ a hormone, a vitamin, ~~thyoxine~~ thyroxine or retinoic acid.

Claim 43. A screening method for unknown ligands of a ~~particular nuclear~~ steroid receptor, wherein an assay method as claimed in claim 36 is employed for the screening.

Claims 44-47. cancelled

Claims 49-53. cancelled

Claims 55-60. cancelled

Claim 61. A kit for use in an assay or screening method ~~as claimed in claim 36,~~ comprising cells as claimed in claim ~~36~~ 19.

Claim 62. A kit for use in an assay, comprising the following constituents:
a) eukaryotic cells wherein ~~tje~~ the intrinsic signal pathway connected to a Ras protein is inactivated in said eukaryotic cell,
b) one or more transformation or transfection vectors ~~which contain~~ comprising at least one DNA sequence which encodes a fusion protein comprising
- a first domain mediates a membrane localization of the fusion protein in a cellular context, wherein the signal of said membrane localization comprises an amino acid sequence which comprises a farnesylation signal or prenylation signal,
- a second domain has a ligand-binding function and comprises an amino acid sequence which comprises the receptor portion of a steroid receptor, and
- a third domain which comprises an amino sequence which comprises a Ras protein that is able to activate a signal pathway connected to a Ras protein in a cell, wherein when there is a lack of binding to the second domain of said fusion protein, the third domain cannot exert its activity to activate a signal pathway connected to a Ras

protein in a cell, despite membrane localization, but when there is binding of ligand to the second domain of said fusion protein, said signalling pathway is activated,

c) optionally comprising reagents for transformation or transfection of the cells with the transformation or transfection vector,

d) optionally comprising reagents for detecting the phenotypical activation of the signal pathway connected to a Ras protein in these cells.

Claims 64-66. cancelled

Claim 71. cancelled

Claims 74-78. cancelled

Claim 81. cancelled

Claim 83. A vector of claim 16 which is a plasmid, cosmid or viral or ~~phase~~ phage genome.

Claim 84. A kit of claim 70 wherein said solid carrier is ~~amicrotitier~~ a microtiter plate or a biochip.

In the specification—

Page 48, beginning at line 30 to page 49, line 33:

In relation to polypeptides or proteins having a ligand-binding function of a receptor and having been derived from a naturally found or synthetically produced molecule for production of the fusion protein ~~as defined in claim I~~ comprising at least three domains, where a first domain mediates membrane localization of the fusion protein in a cellular context, a second domain has or presumably has a ligand-binding function of a nuclear receptor, a third domain has an activity able to activate a signal pathway connected to a Ras protein in a cell, characterized in that when there is a lack of binding or, alternatively, when there is binding of ligand to the second domain the third domain cannot exert its activity to activate a signal pathway connected to a Ras protein in a cell, despite membrane localization, the invention comprises both the fragment which is present in the fusion proteins employed according to the invention and has a ligand-binding function, and the initial fragment or molecule. It may be remarked in relation to this, only for the

sake of clarity, that the production of the fusion protein usually takes place by expression of a nucleic acid sequence encoding this fusion protein in a cell. A polypeptide or protein with ligand-binding function of a receptor is accordingly derived from a larger initial molecule usually in an analogous way at the nucleic acid level, by merely using one or more sections of the nucleic acid sequence encoding the initial molecule, where appropriate with subsequent cloning for attachment of sections which encode other fusion protein components or sections, for expression of the fusion protein. The deriving may also include one or more slight nucleic acid sequence modifications in the initial sequence or in the nucleic acid section(s), preferably of a type such that the resulting nucleic acid molecule still hybridizes under stringent conditions with the respective initial nucleic acid molecule.

The invention accordingly also comprises a method for identifying polypeptides or proteins, in particular receptors, which have a ligand-binding function of a
receptor, which comprises:

- preparing a cell of the invention with a fusion protein ~~having the features described in claim 1~~ comprising at least three domains, where a first domain mediates membrane localization of the fusion protein in a cellular context, a second domain has or presumably has a ligand- binding function of a nuclear receptor, a third domain has an activity able to activate a signal pathway connected to a Ras protein in a cell, characterized in that when there is a lack of binding or, alternatively, when there is binding of ligand to the second domain the third domain cannot exert its activity to activate a signal pathway connected to a Ras protein in a cell, despite membrane localization, and comprising the whole of such a polypeptide or protein or a part of such a polypeptide or protein which presumably contains the sequence sections essential for the ligand-binding function, and
- using this cell to carry out the in vivo assay method of the invention for detecting whether a polypeptide or protein has a ligand-binding function of a nuclear receptor[.],

and the molecules identified by this method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD whose telephone number is 571 272 1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

DCG
Art Unit 1647
12 October 2007

MANJUNATH N. RAO, PH.D.
PRIMARY EXAMINER